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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, JAMES D	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/937,840	SOON-SHIONG ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75-129* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75-129* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/16/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____ .

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 5/16/2008, are acknowledged and entered. Claims 75-129 are pending and under examination.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/16/2008 has been entered.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 5/16/2008. The Examiner has considered the references cited therein to the extent that each is a proper citation. The European Examination Report (Reference 3) was not considered because it is not considered by the Office to be a published document. Please see the attached USPTO Form 1449.

Claim Interpretation

Applicant's disagreement with the Examiner's interpretation of the extent to which "about" modifies the claimed dose ranges is noted. Applicants cite *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.* (Fed. Cir. 2005) for the holding that the ordinary meaning of the term "about" is "approximately". However, the holding in *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.* was simply that the term "about" cannot be construed as "exactly" and must be given its ordinary meaning of "approximately". However, even if the term "about" is construed as "approximately", recitation of "about 1% to about 20%", "about 1% to about 10%", or "about 1% to about 5%" still allow for a broad interpretation of these dose ranges and do not require that the ranges be exactly 1% to 20%, 1% to 10%, or 1% to 5%. In the instant case, absent any definition with respect to the extent that the term "about" modifies the claimed

dose ranges, the Examiner is interpreting the claims to reasonably encompass any percentage of any conventional dose of paclitaxel as long as the dose is functional for its intended purpose.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The rejection of claims 75-89 as failing to comply with the requirements of 35 U.S.C. 101 is withdrawn in light of Applicant's arguments.

Claim Rejections - 35 USC § 112 (2nd Paragraph) - New Grounds of Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 90-129 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(i) Claims 90 and 111 recite the limitation wherein the amount of paclitaxel administered to a subject is "about 1% to about 20%" (claim 90) or "about 1% to about 10%" (Claim 111) of "the conventional dose of paclitaxel over the same period". There is insufficient antecedent basis for this limitation in the claims. By definition, "conventional" means conforming to accepted standards or ordinary. A brief review of the literature suggests that there is more than one accepted standard or ordinary dosing regimen for paclitaxel. For example, the Examiner has found the following dosing regimens of paclitaxel in recent clinical trials:

- 30 mg/m^2 twice a week;
- 50 mg/m^2 on days 1 and 8 of a cycle;
- 70 mg/m^2 weekly for 5 weeks every 6 weeks;
- 80 mg/m^2 weekly for 3 weeks every 4 weeks;
- 175 mg/m^2 by 2 hour infusion on Day 1 every 3 weeks;

- 150 mg/m^2 by 3 hour infusion weekly for 6 weeks;
- 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, or 100 mg/m^2 by 1 hour infusion on days 1, 8, 15, 22, 29, and 36 (every 50 days);
- 100 mg/m^2 on days 1, 8, and 15 of a 28 day cycle;
- 100 mg/m^2 weekly for 3 of 4 weeks; and
- 50 mg/m^2 on days 1, 8, and 15 by *i.v.* infusion.

The doses and administration regimens for paclitaxel vary widely among different patients and conditions and there is no single conventional dose of paclitaxel over any given time period. Accordingly, the metes and bounds of the limitations "about 1% to about 20%" (claim 90) and "about 1% to about 10%" (Claim 111) of "*the conventional dose* of paclitaxel over the same period" cannot be determined. In fact, even over the same period, doses of paclitaxel vary from clinical trial to clinical trial. As such, the claims are indefinite because it is not apparent what doses of paclitaxel are encompassed by the claims. While it appears that it is Applicant's intent that the dose of paclitaxel is less than that previously administered by those skilled in the art, no where in the specification do Applicants provide any specific doses of paclitaxel, other than to say that the dose is "about 1% to about 20%" (claim 90) or "about 1% to about 10%" (Claim 111) of "the conventional dose of paclitaxel over the same period". However, it is clear from the teachings of the prior art regarding administration of paclitaxel to subjects that there is more than one "conventional dose of paclitaxel". The only recitation in the specification of any "conventional dose" of paclitaxel is found at page 7, line 27 to page 8, line 1, which recites that in the "conventional treatment" of cancer utilizing the drug paclitaxel, a dose of about 135-175 mg/m^2 is given every 3 weeks and that the entire dose is given on the first day of the 3 week cycle. However, this dose is clearly different from other doses of paclitaxel that have been administered in the prior art as noted above. Thus, the claims can be interpreted to reasonably encompass any percentage of any conventional dose of paclitaxel when used as chemotherapy, as long as such a dose is functional for its intended purpose.

(ii) Claims 90-129 are further unclear with respect to whether the claimed dose ranges (*e.g.*, about 1% to about 10%) of the conventional dose of paclitaxel over the same period are cumulative doses or individual doses. For example, if the conventional dose is 135-175 mg/m^2 over a period of three weeks (claims 105 and 124), it is not clear if the doses recited in the claims

refer to a total dose over 3 weeks or whether they refer to regular administration of single doses over 3 weeks.

Claim Rejections - 35 USC § 112 – 1st Paragraph – New Grounds of Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 75-89 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn in light of Applicant's arguments. However, a new ground of rejection of claims 75-89 as failing to comply with the written description requirement of 35 U.S.C. 112, first paragraph is set forth below.

The rejection of claims 90-129 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is withdrawn in light of Applicant's arguments. However, a new ground of rejection of claims 90-129 as failing to comply with the written description requirement of 35 U.S.C. 112, first paragraph is set forth below.

Claims 75-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to a method of administering paclitaxel comprising administering paclitaxel to a subject "wherein the plasma level of paclitaxel in the subject is maintained at 0.01 -0.05 μg/mL over a period of 7 days or more".

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to an administration method requiring administration of paclitaxel to a subject in a certain dose range, by a certain administration route, and in a certain administration interval so as to maintain a plasma level of paclitaxel in the subject of 0.01-0.05 μg/mL over a period of 7 days or more.

To provide adequate written description and evidence of possession of claimed subject matter, the specification must provide sufficient distinguishing characteristics of the subject matter.

The specification provides no description of any specific doses, administration routes, or administration regimens that would result in maintenance of the claimed plasma level of paclitaxel over a period of 7 days or more. Other than broad dose ranges (*e.g.*, "about 1% to equal to or about 99%" of the conventionally administered dose), administration routes (*e.g.*, orally, intravenously, locally), and administration intervals (over periods ranging from "about 2 days" to "less than about 365 days"), Applicants provide no description of administration methods that result in maintenance of a plasma level of 0.01-0.05 μg/mL paclitaxel over a period of 7 days or more. It is simply not reasonable to assume that administration of paclitaxel in any dose of about 1% to about 99% of paclitaxel conventionally administered (page 8, lines 11-27), over a period of from about 2 days to less than about 365 days (page 9, lines 11-27), by any administration method, will lead to maintenance of a plasma level of 0.01-0.05 μg/mL paclitaxel over a period of 7 days or more as described by Applicants in the specification. It is noted that Applicants provide no specific examples of any such administration regimens (*e.g.*, administration of 2 mg/m^2 paclitaxel by intravenous infusion for 1 hour every day for 30 days) that result in the plasma level of paclitaxel in the subject being maintained at 0.01-0.05 μg/mL over a period of 7 days or more.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed administration method, which

simply recites "administering paclitaxel to a subject" such that "the plasma level of paclitaxel in the subject is maintained at 0.01-0.05 μg/mL over a period of 7 days or more". One of skill in the art would not recognize from the disclosure that the applicant was in possession of such a method because Applicants have provided no description of any such administration methods that actually result in maintenance of the claimed plasma level of paclitaxel over a period of 7 days or more. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 90-129 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to methods of administering paclitaxel comprising administering paclitaxel to a subject wherein the amount of paclitaxel administered to a subject is "about 1% to about 20%" (claim 90) or "about 1% to about 10%" (Claim 111) of "the conventional dose of paclitaxel over the same period". Other than a dose of about 135-175 mg/m^2 given every 3 weeks, wherein the entire dose is given on the first day of the 3 week cycle (page 7, line 27 to page 8, line 1), Applicants do not have written basis for the claimed "the conventional dose of paclitaxel over the same period". Further, this conventional dose of paclitaxel appears to only be descriptive of a single *i.v.* infusion on day 1 of a 3 week cycle and not other administration routes as broadly encompassed by the claims.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is

whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to an administration method requiring administration of paclitaxel to a subject in certain dose ranges that are defined by a percentage of "the conventional dose of paclitaxel over the same period". To provide adequate written description and evidence of possession of claimed subject matter, the specification must provide sufficient distinguishing characteristics of the subject matter.

The specification provides no description of what "the conventional dose of paclitaxel" is. Other than broad dose ranges (*e.g.*, "about 1% to equal to or about 99%" of the conventionally administered dose), Applicants provide no description of doses of paclitaxel that will be administered to the claimed subjects. By definition, "conventional", as recited in the specification and claims is interpreted by its conventional definition as conforming to accepted standards or ordinary. A brief review of the literature, however, suggests that there is more than one accepted standard or ordinary dosing regimen for paclitaxel. For example, the Examiner has found the following examples of dosing regimens of paclitaxel in recent clinical trials:

- 30 mg/m^2 twice a week;
- 50 mg/m^2 on days 1 and 8 of a cycle;
- 70 mg/m^2 weekly for 5 weeks every 6 weeks;
- 80 mg/m^2 weekly for 3 weeks every 4 weeks;
- 175 mg/m^2 by 2 hour infusion on Day 1 every 3 weeks;
- 150 mg/m^2 by 3 hour infusion weekly for 6 weeks;
- 100 mg/m^2 on days 1, 8, and 15 of a 28 day cycle;
- 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, or 100 mg/m^2 by 1 hour infusion on days 1, 8, 15, 22, 29, and 36 (every 50 days);
- 100 mg/m^2 weekly for 3 of 4 weeks; and
- 50 mg/m^2 on days 1, 8, and 15 by i.v. infusion.

Thus, there appears to be more than one "conventional dose" of paclitaxel because the doses and administration regimens for paclitaxel vary widely among different patients and conditions. Accordingly, Applicants have not described the claimed amounts of paclitaxel or "the conventional dose of paclitaxel" in a manner that would indicate that they were in possession of the claimed invention. Describing the amounts of paclitaxel as "about 1% to about 20%" (claim

90) or "about 1% to about 10%" (Claim 111) of "the conventional dose of paclitaxel over the same period" does not provide a description of how much paclitaxel is intended to be administered in the claimed methods or what the conventional dose of paclitaxel is. This lack of written description is further compounded by the fact that, even over the same period, doses of paclitaxel vary from clinical trial to clinical trial. While it appears that it is Applicant's intent that the dose of paclitaxel is less than that previously administered by those skilled in the art, no where in the specification do Applicants provide any specific doses of paclitaxel, other than to say that the dose is "about 1% to equal to or about 99%" of "the conventionally administered dose", "about 1% to about 20%" (claim 90) or "about 1% to about 10%" (Claim 111) of "the conventional dose of paclitaxel over the same period". Further, paclitaxel is normally administered by intravenous infusion whereas the claims encompass administration of paclitaxel by any means. As such, Applicants have also failed to describe what the "conventional dose" of paclitaxel is when it is administered by routes other than intravenous infusion.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed "the conventional dose of paclitaxel" or amounts of paclitaxel that can be administered "over a period of 7 days or more" to maintain a therapeutically effective plasma level of paclitaxel throughout the period of 7 days or more. One of skill in the art would not recognize from the disclosure that the applicant was in possession of such amounts of paclitaxel because Applicants have provided no description of any such amounts that actually result in maintenance of the claimed plasma level of paclitaxel over a period of 7 days or more. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 90-91, 93-95, 97-98, 100, 103, 105-114, 116-117, 119, 122, and 124-129 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Chang *et al***. (Reference 55 on IDS filed 9/7/2007).

The instant claims recite methods of administering paclitaxel comprising administering paclitaxel over a period of "7 days or more", wherein the amount of paclitaxel is "*about* 1% to *about* 20% of the conventional dose" of paclitaxel (claim 90) or "*about* 1% to *about* 10% of the conventional dose" of paclitaxel (claim 111).

Chang *et al*. teach a dose escalation study of paclitaxel wherein patients were treated with a one-hour infusion of paclitaxel weekly for 3 weeks. An infusion meets the limitation "systemically" and "intravenously" as recited in claims 95, 97, 114, and 116. A "one-hour infusion" meets the limitation "continuously" as recited in claims 106 and 125. The administration of paclitaxel weekly for 3 weeks meets the limitations of claims 107-109 and 126-128, which recite administration over periods of less than one year, less than 3 months, and less than one month. With respect to dose, Chang *et al*. administered paclitaxel at a dose of 50 mg/m^2/week, increasing 10 mg/m^2/week every five patients. These doses meet the limitation of claims 105 and 124, which recite a conventional dose of paclitaxel of 135-175 mg/m^2 over a period of three weeks.

Applicant's arguments have been considered but they are not deemed to be persuasive. Applicants argue that the dose levels of Chang et al. are "well above" the conventional doses of paclitaxel as recited in the present claims. However, a dose of 50 mg/m^2/week is reasonably a percentage of a conventional dose of paclitaxel that is still functional for its intended purpose and thus anticipates the claimed dose ranges. As discussed *supra*, the claims reasonably encompass administering a dose of paclitaxel that is any percentage of any conventionally administered dose of paclitaxel as long as such a dose is functional for its intended purpose. Applicants further argue that Chang is silent about "maintaining a therapeutically effective plasma level of paclitaxel throughout the period of 7 days or more". However, in the absence of evidence to the contrary, the Examiner is not persuaded that administration of 50 mg/m^2/week paclitaxel will not

result in a therapeutically effective plasma level of paclitaxel throughout the period of 7 days or more as instantly claimed.

Accordingly, the claims are deemed properly rejected as being anticipated by Chang *et al*.

Claims 90-95, 97-98, 100, 103, 105-108, 110-114, 116-117, 119, 122, 124-127, and 129 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Klaassen *et al***. (Reference A28 on IDS filed 5/12/2003).

The instant claims recite methods of administering paclitaxel comprising administering paclitaxel over a period of "7 days or more", wherein the amount of paclitaxel is "about 1% to about 20% of the conventional dose" of paclitaxel (claim 90) or "about 1% to about 10% of the conventional dose" of paclitaxel (claim 111).

Klaassen *et al*. teach administration of paclitaxel via a 1-hour infusion on days 1, 8, 15, 22, 29, and 36 (every 50 days) at dose levels of 70 mg/m^2, 80 mg/m^2, 90 mg/m^2, and 100 mg/m^2, thus meeting the limitations of claims 90-95, 97, 105-108, 110-114, 116, 124-127, and 129.

Applicant's arguments have been considered but they are not deemed to be persuasive. Applicants argue that the dose levels of Klassen et al. are "well above" the conventional doses of paclitaxel as recited in the present claims. However, the doses administered in Klassen are reasonably a percentage of a conventional dose of paclitaxel that is still functional for its intended purpose and thus anticipates the claimed dose ranges. As discussed *supra*, the claims reasonably encompass administering a dose of paclitaxel that is any percentage of any conventionally administered dose of paclitaxel as long as such a dose is functional for its intended purpose. Applicants further argue that Klassen is silent about "maintaining a therapeutically effective plasma level of paclitaxel throughout the period of 7 days or more. However, in the absence of evidence to the contrary, the Examiner is not persuaded that administration of the doses of paclitaxel taught in Klassen will not result in a therapeutically effective plasma level of paclitaxel throughout the period of 7 days or more as instantly claimed.

Accordingly, the claims are deemed properly rejected as being anticipated by Klassen *et al*.

Claims 90-95, 97-98, 100, 103, 105-108, 110-114, 116-117, 119, 122, 124-127, and 129 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Fennelly *et al***. (Reference A16 on IDS filed 5/12/2003).

The instant claims recite methods of administering paclitaxel comprising administering paclitaxel over a period of "7 days or more", wherein the amount of paclitaxel is "about 1% to about 20% of the conventional dose" of paclitaxel (claim 90) or "about 1% to about 10% of the conventional dose" of paclitaxel (claim 111).

Fennelly *et al*. teach administration of paclitaxel in doses of 40, 50, 60, 80, and 100 mg/m^2 to ovarian cancer patients (Abstract). These doses anticipate the instantly claimed doses of "*about* 1 % to *about* 20% of the conventional dose of paclitaxel" (claim 90) and "*about* 1 % to *about* 10% of the conventional dose of paclitaxel" (claim 111). Paclitaxel was administered via a 1-hour infusion thus anticipating the instantly claimed "systemically" and "intravenously" as recited in claims 95, 97, 114, and 116 (*id*.). A "one-hour infusion" also meets the limitation "continuously" as recited in claims 106 and 125. The infusions were administered "weekly" for an average of 10 weeks thus meeting the limitations of claims 91-92, 107-108, 112, and 126-127 (*id*.).

Applicant's arguments have been considered but they are not deemed to be persuasive. Applicants argue that the dose levels of Fennelly et al. are "well above" the conventional doses of paclitaxel as recited in the present claims. However, the doses administered in Fennelly are reasonably a percentage of a conventional dose of paclitaxel that is still functional for its intended purpose and thus anticipates the claimed dose ranges. As discussed *supra*, the claims reasonably encompass administering a dose of paclitaxel that is any percentage of any conventionally administered dose of paclitaxel as long as such a dose is functional for its intended purpose. Applicants further argue that Fennelly is silent about "maintaining a therapeutically effective plasma level of paclitaxel throughout the period of 7 days or more. However, in the absence of evidence to the contrary, the Examiner is not persuaded that administration of the doses of paclitaxel taught in Fennelly will not result in a therapeutically effective plasma level of paclitaxel throughout the period of 7 days or more as instantly claimed. With respect to Applicant's argument that Fennelly is silent about "regularly administering" paclitaxel over a period of 7 days or more, no where do Applicants define what "regularly

administering" means. As such, a 1 hour infusion reasonably anticipates regular administration over 7 days or more because there is no evidence of record that therapeutic levels of paclitaxel are not present in the body after 7 days or more after weekly 1 hour infusions.

Accordingly, the claims are deemed properly rejected as being anticipated by Fennelly *et al*.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 99, 101, 118, and 120 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Fennelly *et al***. as applied to claims 90-95, 97-98, 100, 103, 105-108, 110-114, 116-117, 119, 122, 124-127, and 129 above, and further in view of **WO 98/14174** (Published April 9, 1998) (Reference 46 on IDS filed 9/4/2007).

Instant claims 99, 101, 118, and 120 recite administration of paclitaxel in a slow release delivery vehicle and/or a colloidal dispersion system comprising nanocapsules.

Fennely *et al*. teach as discussed *supra*. The reference does not teach the administration of paclitaxel in a colloidal dispersion system comprising nanocapsules or a slow release delivery vehicle.

However, WO '174 teaches compositions and methods for the *in vivo* delivery of substantially insoluble pharmacologically active agents (such as paclitaxel) in which the active agent is delivered in the form of suspended particles coated with a protein (Abstract). The particulate system of the invention can be converted into a redispersible dry powder comprising **nanoparticles** of water-insoluble drug coated with a protein, and free protein to which molecules of the active agent are bound (*id.*). Invention colloidal systems may be prepared without the use of conventional surfactants and in a preferred embodiment, the invention methods is used to prepare extremely small particles which can be sterile-filtered (page 1, lines 13-18). The nanoparticles of the invention provide a pre-programmed duration of action, ranging from days to weeks to months from a single injection, thus meeting the limitation "slow release delivery vehicles" as recited in claims 99 and 118 (page 2, lines 14-16).

Thus, it would have been *prima facie* obvious to one ordinary skill in the art to administer paclitaxel in nanoparticles in order to provide a pre-programmed duration of action and to decrease toxicity associated with conventional paclitaxel administration methods.

The prior art teaches methods of administering paclitaxel comprising administering paclitaxel in doses of 40, 50, 60, 80, and 100 mg/m^2 via a 1-hour infusion weekly for 10 weeks. The prior art also motivates and suggests administering paclitaxel in nanoparticles in order to provide a pre-programmed duration of action and to decrease toxicity associated with conventional paclitaxel administration methods.

The prior art does not explicitly teach administering paclitaxel in nanoparticles or in a slow release delivery vehicle using the administration regimen instantly claimed.

The level of ordinary skill in the art is high, generally that of a Ph.D. or M.D. with at least several years of experience in drug delivery methods.

There is no evidence of record that one skilled in the art would not have found the instantly claimed delivery vehicles *prima facie* obvious. Slow release delivery vehicles and colloidal dispersion systems such as nanoparticles are routinely used to deliver pharmacologically active agents. Accordingly, use of these vehicles to deliver paclitaxel would have been obvious to the skilled artisan. At the time of the invention, there was a recognized need in the art – that being an administration regimen for paclitaxel that would be clinically effective and at the same time non-toxic. One skilled in the art is faced with a finite number of

predictable solutions for delivering paclitaxel to human patients. For example, one could modify the administration schedule (*i.e.*, longer or shorter duration between infusions), dose (*i.e.*, higher or lower doses), and/or length of infusion (*i.e.*, longer or shorter infusion duration). Further, delivery vehicles for administration of pharmacologically active agents are limited in number (*e.g.*, aqueous solutions, emulsions, liposomes, tablets, etc.). Given the finite number of predictable solutions for delivering active agents, one skilled in the art could have pursued the known options within his or her technical grasp with a reasonable expectation of success. In other words, one skilled in the art could readily formulate paclitaxel in a slow release delivery vehicle or in nanoparticles and administered these formulations to patients with a reasonable expectation that the formulations would have been clinically effective.

Applicant's arguments have been considered but they are not persuasive. Applicants argue that Fennelly does not teach or suggest administering paclitaxel at about 1% to about 20% (or about 1% to about 10%) of the conventional dose over a period of 7 days or more. The Examiner refers to his discussion *supra* with respect to these dose ranges. WO '174 is only provided as evidence that delivery of pharmacologically active agents in the form of suspended particles or nanoparticles was known in the art.

Claims 99-104 and 118-123 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Fennelly *et al***. as applied to claims 90-95, 97-98, 100, 103, 105-108, 110-114, 116-117, 119, 122, 124-127, and 129 above, and further in view of **U.S. Patent No. 6,211,171** (Issued Apr. 3, 2001; Filed May 19, 1998).

Instant claims 99-104 and 118-123 recite administration of paclitaxel in a slow release delivery vehicle, a colloidal dispersion system, in a polymer of stabilized crystals and in colloidal dispersion systems comprising nanocapsules, microspheres, liposomes, or oil-in-water emulsions.

Fennely *et al*. teach as discussed *supra*. The reference does not teach the administration of paclitaxel in a slow release delivery vehicle, in a polymer of stabilized crystals or in colloidal dispersion systems comprising nanocapsules or microspheres

However, U.S. '171 teaches methods for the *in vivo* delivery of antidepressants (Abstract). At column 11, lines 1-17, compositions formulated for local injections are taught

which generally comprise a physiologically compatible saline solution and may optionally be encapsulated in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals. Colloidal dispersion systems include nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. The preferred colloidal system of this invention is a liposome or microsphere. Liposomes are artificial membrane vesicles which are useful as slow release delivery vehicles when injected or implanted, or when contained within a topical preparation.

Thus, it would have been *prima facie* obvious to one ordinary skill in the art to formulate paclitaxel in a composition suitable for local injection, such as those compositions taught in U.S. '171.

The prior art teaches methods of administering paclitaxel comprising administering paclitaxel in doses of 40, 50, 60, 80, and 100 mg/m^2 via a 1-hour infusion weekly for 10 weeks. The prior art also teaches compositions suitable for local injection of active agents comprising a physiologically compatible saline solution and may optionally be encapsulated in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals.

The prior art does not explicitly teach administering paclitaxel in a colloidal dispersion system or in polymer-stabilized crystals using the administration regimen instantly claimed.

The level of ordinary skill in the art is high, generally that of a Ph.D. or M.D. with at least several years of experience in drug delivery methods.

There is no evidence of record that one skilled in the art would not have found the instantly claimed delivery vehicles *prima facie* obvious. Compositions formulated for local injections, which generally comprise a physiologically compatible saline solution and may optionally be encapsulated in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals were known in the art. Such colloidal dispersion systems include nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes as instantly claimed. Accordingly, use of these vehicles to deliver paclitaxel would have been obvious to the skilled artisan. At the time of the invention, there was a recognized need in the art – that being an

administration regimen for paclitaxel that would be clinically effective and at the same time non-toxic. One skilled in the art is faced with a finite number of predictable solutions for delivering paclitaxel to human patients. For example, one could modify the administration schedule (*i.e.*, longer or shorter duration between infusions), dose (*i.e.*, higher or lower doses), and/or length of infusion (*i.e.*, longer or shorter infusion duration). Further, delivery vehicles for administration of pharmacologically active agents are limited in number (*e.g.*, aqueous solutions, emulsions, liposomes, tablets, etc.). Given the finite number of predictable solutions for delivering active agents, one skilled in the art could have pursued the known options within his or her technical grasp with a reasonable expectation of success. In other words, one skilled in the art could readily formulate paclitaxel in a slow release delivery vehicle suitable for local injection, such as a colloidal dispersion system or in polymer stabilized crystals, and administered these formulations to patients with a reasonable expectation that the formulations would have been clinically effective.

Applicant's arguments have been considered but they are not persuasive. Applicants argue that Fennelly does not teach or suggest administering paclitaxel at about 1% to about 20% (or about 1% to about 10%) of the conventional dose over a period of 7 days or more. The Examiner refers to his discussion *supra* with respect to these dose ranges. U.S. '171 is only provided as evidence that compositions formulated for local injections comprising a physiological compatible saline solution optionally encapsulated in a slow release delivery vehicle, including a colloidal dispersion system (e.g. nanocapsules) or in polymer stabilized crystals were known in the art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225

USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

U.S. Non-Provisional Application No. 11/644,850

Claims 90-98, 105-117, and 124-129 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/644,850. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed methods of the 11/644/850 patent fully encompass the instantly claimed subject matter and are generic to the claimed methods of administration.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's request that the Examiner hold this provisional rejection in abeyance until the Office has made a determination of otherwise allowable claims in the present application or in co-pending application No. 11/644,850 is noted. As no allowable claims in either application have been determined, the rejection is maintained for the reasons of record.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614